Pharmacology Biochemistry & Behavior, Vol. 35, pp. 443–450. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Reinforcing Effects of a Pentobarbital-Ethanol Combination Relative to Each Drug Alone[1]

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Received 24 May 1989

MEISCH, R. A. AND G. A. LEMAIRE. *Reinforcing effects of a pentobarbital-ethanol combination relative to each drug alone.* PHARMACOL BIOCHEM BEHAV **35**(2) 443–450, 1990.—The reinforcing effects of an orally delivered combination of 1 mg/ml pentobarbital plus 1% ethanol were evaluated in four rhesus monkeys. The drug combination and another liquid (either water, 1 mg/ml pentobarbital, or 1% ethanol) were concurrently available under identical fixed-ratio (FR) schedules. Substantially higher response rates were maintained by the drug combination than by any of the three other liquids. Thus, the reinforcing effects of the pentobarbital-ethanol combination were greater than those of either component drug. In a second experiment, water (the vehicle) was concurrently available with one other liquid (1 mg/ml pentobarbital, 1% ethanol, or the pentobarbital-ethanol combination). All three drug solutions functioned as reinforcers since they maintained much higher response rates than water. These results demonstrate that the greater relative reinforcing effects of the drug combination in the first experiment were not due to a lack of reinforcing effects of the 1 mg/ml pentobarbital or 1% ethanol solutions. In a final experiment, the drug combination was scheduled concurrently with 1 mg/ml pentobarbital, and FR size was systematically varied. The drug combination was then scheduled concurrently with 1% ethanol, and FR size was again varied. As FR size increased, the relative amount of responding maintained by the drug combination increased. Thus, differences in relative reinforcing effects that were evident in the first experiment were again evident in the final experiment when appropriate schedule-parameter values were used.

Polydrug abuse Alcohol-barbiturate combination Ethanol/alcohol Pentobarbital Drug reinforcement
Drug interactions Fixed-ratio schedules Concurrent schedules Relative reinforcing effects Oral route
Rhesus monkeys

POLYDRUG abuse is a serious and common problem (10), and an important form of polydrug abuse is the combination of ethanol with other drugs (16). Ethanol is frequently combined with other CNS general depressants such as barbiturates. Additive or greater than additive effects have often been reported for barbiturate-ethanol combinations. However, sleep time or motor performance have usually been studied [see (4)] rather than self-administration. Moreover, the enhanced effects of drug combinations on one behavior may not be predictive of their effects on other behaviors. The effects of drug combinations can vary depending upon the variable that is measured. For example, in mice ethanol-pentobarbital combinations produced a greater shift in the dose-response curve for the loss-of-righting reflex than for lethality (18). Since the quantitative effects of drug combinations on one behavior may differ from their quantitative effects on other behaviors, the behavior of interest needs to be directly examined. In the present study we examined the self-administration of a pentobarbital-ethanol combination and compared the reinforcing effects of the drug combination to those produced by either drug alone.

Although the desirability of behavioral testing of drug interactions has been noted (2,7), there are few reports in the literature concerning possible increases in reinforcing effects due to coadministration of two reinforcing drugs. In one study with a single rhesus monkey, a combination of pentobarbital and d-amphetamine served as the reinforcer. The subject self-administered nearly twice as many intravenous injections of this drug combination than of either of the drugs alone (19). In another study intravenous injections of combinations of low pentobarbital doses and low ethanol doses maintained lever pressing in rats; neither low doses of pentobarbital nor low doses of ethanol maintained behavior when given alone (3). In establishing orally delivered pentobarbital as a reinforcer for rhesus monkeys, we have noted that under some conditions the addition of small amounts of ethanol to a pentobarbital solution produces unexpectedly en-

[1]This research was conducted while the authors were at the University of Minnesota and was supported by Grant DA 00944 from the National Institute on Drug Abuse. G. A. Lemaire received support from NIDA Training Grant 5T32 DA 07097.
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hanced intake (unpublished observations). The purpose of the present experiments was to follow-up these initial observations by systematically investigating the reinforcing effects of an ethanol-pentobarbital combination.

Since absolute response rates can be a misleading indicator of reinforcing effects, paradigms that utilize relative rates of behavior are often more appropriate (9, 11, 12, 17). Two such paradigms that have been used with pentobarbital reinforced behavior are relative changes in the number of fixed ratios completed as FR size increases (11,12), and relative response rates under concurrent schedules of access to two drug solutions (14,15). The latter paradigm was used in the first two phases of the present study, and in the final phase both paradigms were used within a single procedure to analyze the relative reinforcing effects of a pentobarbital-ethanol combination.

METHOD

Animals

Four adult male rhesus monkeys (*Macaca mulatta*) were housed in experimental chambers in a room illuminated 12 hr daily and maintained at 26.5°C. All four monkeys (M-P1, M-A, M-C, and M-CR) had histories of oral ethanol and pentobarbital reinforced behavior, and for six or more years all four had participated in daily 3-hr test sessions where ethanol and/or pentobarbital were available. Mean body weights were: M-P1, 6.5 kg; M-A, 10.1 kg; M-C, 8.8 kg; and M-CR, 9.7 kg; these weights were 80%, 82%, 77%, and 72% of subjects' free-feeding weights. In our laboratory, where the monkeys are housed individually in cages, unlimited access to food results in the development of obesity in some animals. Thus, free-feeding weights under our laboratory conditions do not necessarily reflect free-feeding weights under more natural conditions. The monkey maintained at the lowest percentage of its free-feeding weight (M-CR) had reached an obese, 13.4-kg weight under free-feeding conditions, and at its maintenance weight was still nearly as large as the heaviest subject. The maintenance weights do not represent a marked degree of food deprivation, and the monkeys' health and appearance were normal during the experiments. The monkeys' health was monitored daily by veterinary-care personnel.

Apparatus

Stainless-steel primate cages (Hoeltge, No. HB-108) having three solid walls and one barred wall served as experimental and living chambers. On one solid wall each cage was equipped with two spouts and corresponding stimulus lights. The spouts were used to dispense liquid and were constructed entirely of brass and, therefore, electrically conductive at any point of contact. The two spouts were located 30.3 cm apart, and protruded 2 cm into the cage. Lip contacts on a drinking spout activated a solenoid for a maximum duration of 0.15 sec and delivered approximately 0.65 ml of liquid. A break in contact during liquid delivery resulted in termination of solenoid operation, thus preventing spillage. The lip contacts with the spouts were the operant responses, and typical response topographies have been described (12). Liquid availability was signaled by illumination of green stimulus lights located 12 cm above the drinking spouts. During sessions, the green stimulus light above each spout blinked at the rate of 10 Hz. Between sessions, the green light was steadily illuminated above the spout that delivered water (see below). Two pairs of feedback stimulus lights were located behind a Plexiglas plate which surrounded each drinking spout. One pair was covered with white lenses, and the other pair was covered with green lenses. During sessions responses on either spout activated that spout's green lights, and between sessions responses illuminated the white lights at the spout that delivered water. Each mouth contact with the spout illuminated the appropriate pair of lights (white or green) for the duration of the response. During sessions the temporal pattern of responses and deliveries was continuously recorded by cumulative recorders and by print-out counters that printed the data every ten minutes. Details of the apparatus and drinking device have been described elsewhere (6,13). Solid-state programming equipment (Coulbourn Instruments, Inc.) located in an adjacent room was used for scheduling experimental events and for numerically recording responses.

Drugs

Solutions of sodium pentobarbital were mixed in tap water approximately 3 hr prior to each session and were presented at room temperature. Pentobarbital concentration is expressed in terms of the salt, and the ethanol percentage is weight to volume.

Procedure

Daily experimental sessions were 3 hr in duration and were conducted seven days a week at a regular starting time (10:00 a.m.). All sessions were preceded and followed by a 1-hr stimulus blackout during which the number of mouth-contact responses, liquid deliveries, and milliliters of liquid consumed were recorded, and solutions were changed. Following the 1-hr postsession stimulus blackout, intersession access to water occurred for 1 hr. This 1 hr of water access was followed by another 1 hr blackout during which the monkeys were given their daily ration of Purina High Protein Monkey Chow. Subsequent to this, there was an uninterrupted 17-hr period of access to water under a fixed-ratio 1 (FR 1) schedule. The side location of water was alternated such that during one intersession period it was available from the right spout and during the next it was available from the left spout. As noted above, water access during intersession periods was indicated by steady illumination of the green stimulus light above the spout.

During sessions two liquids were concurrently available, one liquid from each spout. The spout at which a particular liquid was available alternated between the left and right sides from one session to the next. The liquids available were always two from among the following four: water, a 1% (w/v) ethanol solution, a 1 mg/ml pentobarbital solution, or a "combination" solution containing both 1% ethanol and 1 mg/ml pentobarbital. Since all monkeys had previous histories of oral pentobarbital- and ethanol-reinforced behavior, high rates of responding were promptly established. Each condition was studied until visual inspection of the data revealed no systematic trends over six consecutive sessions in either the rate or pattern of responding.

Concurrent access to the drug combination and either water, ethanol, or pentobarbital. During the first phase of the study the drug combination (1 mg/ml pentobarbital plus 1% ethanol) and another liquid were presented concurrently under FR schedules. The liquids concurrently available with the drug combination were presented in the following sequence to counterbalance for order effects: water, pentobarbital (1 mg/ml), ethanol (1%), water, ethanol (1%), pentobarbital (1 mg/ml), and water. The FR values for each monkey were: M-A and M-P1, FR 16; M-C and M-CR, FR 8 (M-A and M-P1 were tested at FR 16 because at FR 8 water-maintained responding was too high, relative to drug-maintained responding, to be acceptable for the purposes of the study).

Concurrent access to water and either the drug combination, pentobarbital, or ethanol. During the second phase of the study water and another liquid were presented concurrently. Fixed-ratio

sizes were the same as in the previous phase. The liquids concurrently available with water were presented in the following order: drug combination (1 mg/ml pentobarbital plus 1% ethanol), pentobarbital (1 mg/ml), ethanol (1%), and drug combination. Because the initial test condition of this series was identical to the final test condition of the previous series (viz. concurrent access to the drug combination and water), the same data were used for both the final condition of the previous phase and the initial condition of this phase (i.e., the condition was not repeated).

Fixed-ratio size as a determinant of relative rates of behavior: Concurrent scheduling of the drug combination and either ethanol or pentobarbital. Two sequences of manipulations were conducted in the third, and final, phase of the study. In the first sequence, the drug combination (1 mg/ml pentobarbital plus 1% ethanol) was concurrently present with 1 mg/ml pentobarbital. Fixed-ratio value was decreased and then increased, with six sessions of stable data obtained at each FR size. For monkeys M-A and M-P1, the order of these changes was FR 16, 8, 4, 2, 1, 2, 4, 8, and 16. For monkeys M-C and M-CR the order was FR 8, 4, 2, 1, 2, 4, and 8. In the second sequence of this final phase, the drug combination was concurrently present with 1% ethanol, and the same sequences of FR sizes were tested as with pentobarbital (for a reason explained below, an additional, final test was conducted with M-P1 at FR 32).

At low FR values large amounts of drug could be consumed rapidly, and, thus, the monkeys could potentially overdose and die. To prevent overdoses, a "limiter" was programmed into the control equipment which inserted a 20-min time-out period into a subject's session if that subject obtained a predetermined number of deliveries within a 20-min interval. The limit was not set timidly; it permitted the monkey to obtain sufficient drug quantities to leave it briefly anesthetized. The upper limits to the number of deliveries possible within a given drinking bout were set according to individual subjects' characteristic responses to drug (M-A, 300; M-C, 350; M-CR, 350; and M-P1, 250 deliveries). For example, if Monkey M-A obtained 300 deliveries within any single drinking bout, a time-out was initiated (a single bout was defined as a sequence of drug deliveries during which no pause of at least 20 min occurred). On the other hand, the monkey potentially could take 275 deliveries, pause 20 min, and then take another 275 deliveries without initiating the time-out. The limiters were actually activated only at low FR sizes, and then only occasionally. Typically, subjects' drinking bouts were self-limited.

RESULTS

The "break and run" pattern of responding maintained by drug deliveries in all phases of the study was characteristic of responding usually observed under fixed-ratio schedules [i.e., a pause in responding following a reinforcer delivery, followed by a sustained rate of responding until the next reinforcer delivery; for representative cumulative records of behavior maintained by pentobarbital and a pentobarbital-ethanol combination, see (11,12)]. The time course of responding was also similar to that previously reported when either pentobarbital or ethanol served as reinforcers: the highest rate was at the beginning of the session, and the initial bout of responding was followed by a pause and then by a smaller bout or bouts later in the session.

Concurrent Access to the Drug Combination and Either Water, Ethanol, or Pentobarbital

Figure 1 shows that for all four monkeys the combination of 1 mg/ml pentobarbital and 1% ethanol was strongly preferred to the three alternative solutions—water (the vehicle), pentobarbital alone (1 mg/ml), and ethanol alone (1%). For three monkeys (M-A, M-C, and M-CR), the alternative solutions maintained negligible rates of responding (few deliveries were obtained). Monkey M-P1 obtained over 150 deliveries of 1% ethanol when it was first available (during the third test condition in the series). However, this was less than the number of deliveries of the drug combination. When this monkey was subsequently retested with the same two solutions during the reverse test sequence (the fifth condition in the series), the number of ethanol deliveries was markedly less, whereas the number of drug combination deliveries remained high and essentially unchanged from its initial test value. When retests of the baseline conditions were conducted (i.e., drug combination versus the water vehicle), deliveries of the combination and the water vehicle were similar to the initial test values. Drug intakes during the final condition of this phase, in which the drug combination was concurrently available with water, were as follows: Mean pentobarbital intakes were 29.7, 16.3, 29.4, and 23.2 mg of pentobarbital per kg of body weight per session for monkeys M-P1, M-A, M-C, and M-CR, respectively. A 1% (w/v) ethanol solution consists of 10 mg of ethanol per milliliter. Since the ethanol concentration (10 mg/ml) was ten times the pentobarbital concentration (1 mg/ml), the intakes of ethanol were ten times those of pentobarbital (i.e., 297, 163, 294, and 232 mg/kg for monkeys M-P1, M-A, M-C, and M-CR, respectively).

Concurrent Access to Water and Either the Drug Combination, Pentobarbital, or Ethanol

A possible explanation for the preference of the drug combination over both 1% ethanol and 1 mg/ml pentobarbital in the first set of manipulations is that ethanol and pentobarbital were not themselves reinforcers. However, Fig. 2, which depicts the outcome of the second phase of the study, shows that pentobarbital at a concentration of 1 mg/ml and ethanol at a concentration of 1% did indeed serve as reinforcers for the four monkeys, since both pentobarbital and ethanol maintained substantially higher rates of behavior than the concurrently available water vehicle. For three of the monkeys (M-P1, M-C, and M-CR), the number of pentobarbital deliveries when 1 mg/ml pentobarbital was concurrently available with water almost equalled the number of deliveries of the drug combination when the combination was available with water, and always exceeded the number of deliveries of 1% ethanol obtained when the ethanol solution was available with water. For Monkey M-A, the number of pentobarbital deliveries was low; the number of ethanol deliveries was higher, but less than the number of deliveries of the drug combination. Figure 2 also shows that the values for the baseline condition (drug combination versus water) were similar before and after the individual tests of pentobarbital and ethanol. This constancy of baseline values demonstrates that the decreases seen when the single drugs were available were not due to nonspecific decreases over time in drug-maintained responding.

Fixed-Ratio Size as a Determinant of Relative Rates of Behavior: Concurrent Scheduling of the Drug Combination and Either Ethanol or Pentobarbital

Figure 3 illustrates the results as FR size was manipulated with 1 mg/ml pentobarbital concurrently available with the drug combination, and Fig. 4 shows the results when 1% ethanol and the drug combination were concurrently available. In this third set of manipulations, the number of 1% ethanol deliveries increased for all subjects as FR size was decreased (Fig. 4). The same was true with two subjects (M-A and M-C) for deliveries of 1 mg/ml

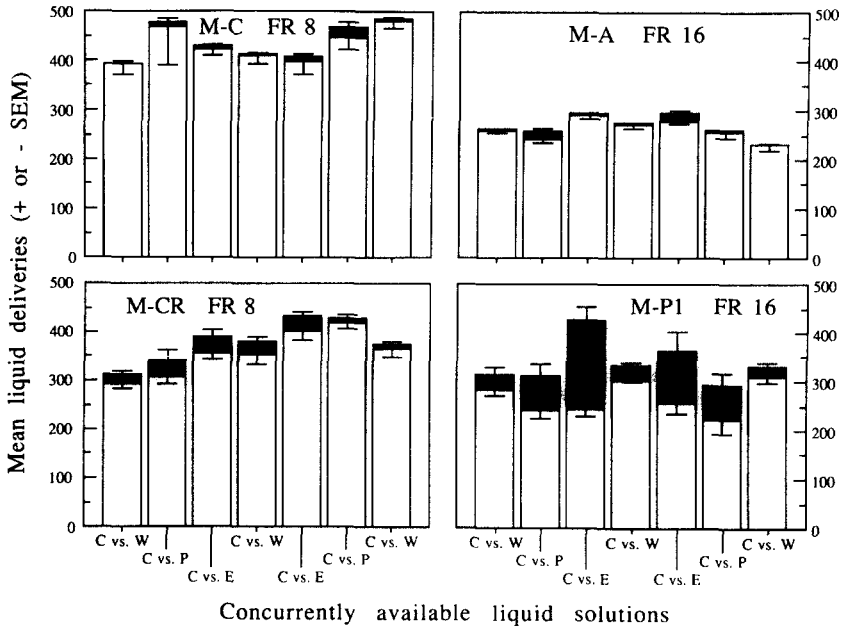

FIG. 1. Mean (n = 6) liquid deliveries per 3-hr session for the drug combination (1 mg/ml pentobarbital plus 1% ethanol) and a concurrently available liquid: either water, 1 mg/ml pentobarbital, or 1% (w/v) ethanol. Abbreviations: C = combination of pentobarbital and ethanol; W = water; P = pentobarbital; E = ethanol. Empty portion of bars: deliveries of drug combination. Filled portion of bars: deliveries of concurrently available liquid. The bars are stacked, not overlaid; thus, deliveries of W, P, or E are represented solely by the filled bar, and not by the sum of the open and filled bars. Test conditions were conducted in the sequence in which the results are depicted (left to right).

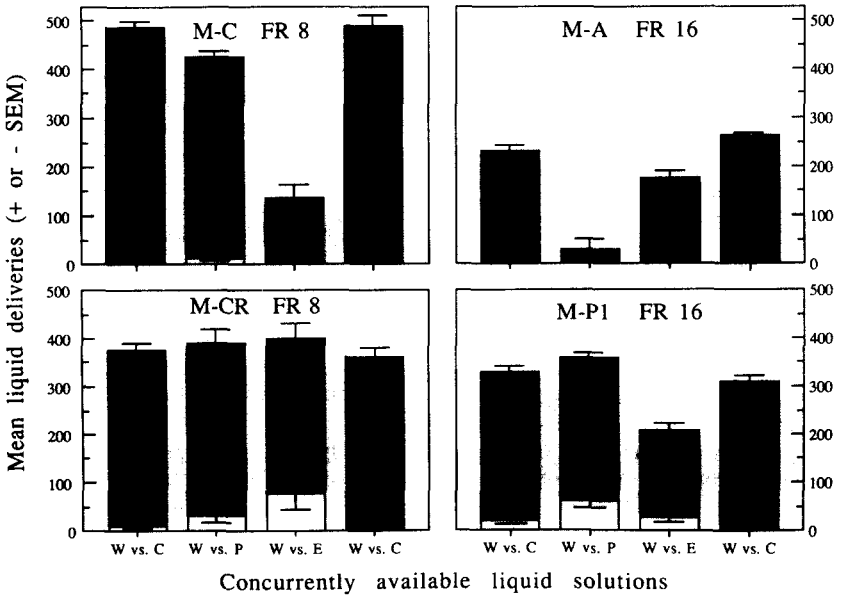

FIG. 2. Mean (n = 6) liquid deliveries per 3-hr session for the water vehicle (W) and a concurrently available liquid: either the drug combination (C), 1 mg/ml pentobarbital (P), or 1% ethanol (E). Empty portion of bars: deliveries of water. Filled portion of bars: deliveries of the concurrently available liquid. Note that the bars are stacked, not overlaid. Test conditions were conducted in the sequence in which the results are depicted (left to right).

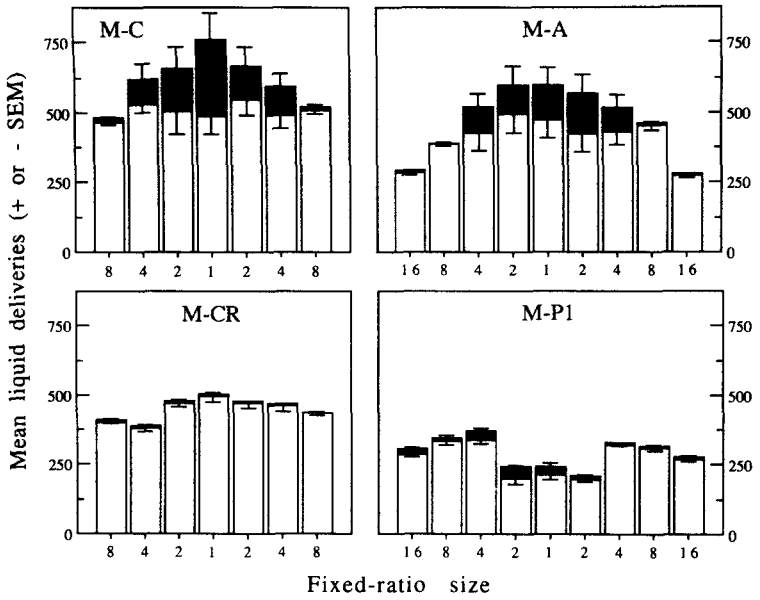

FIG. 3. Mean deliveries (n=6) of the drug combination (open bars) and 1 mg/ml pentobarbital (filled bars) per 3-hr session as a function of fixed-ratio size. At each condition the two liquids were concurrently available under independent FR schedules of equal size. Note that the bars are stacked, not overlaid. Test conditions were conducted in the same sequence depicted (left to right).

pentobarbital (Fig. 3). For monkeys M-A and M-C, when FR size was increased again the number of deliveries of both alternate liquids (first 1 mg/ml pentobarbital and then 1% ethanol) generally decreased in an orderly fashion that was the mirror image of the results seen when FR size was decreased. With all subjects, deliveries of these alternative liquids generally constituted an increasing percentage of the total number of liquid deliveries as FR size decreased (the major exception occurred with M-CR when 1 mg/ml pentobarbital was concurrently available with the drug combination). Another way of stating this is that the difference in

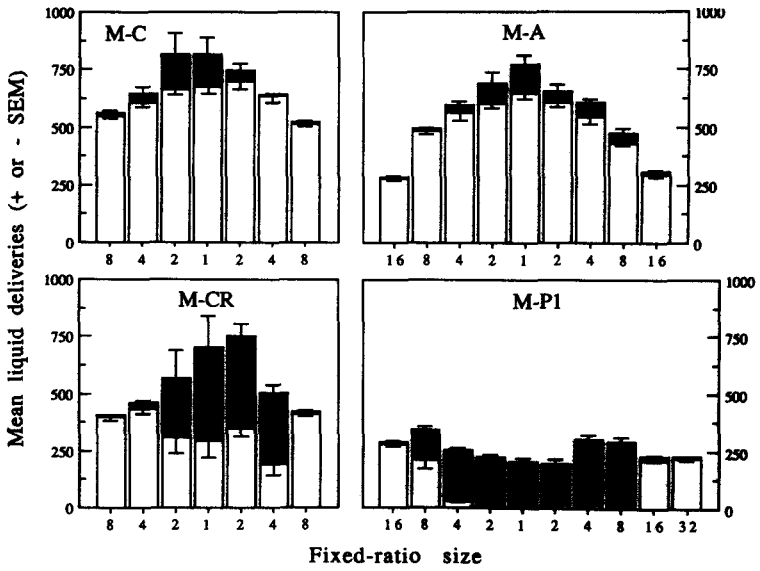

FIG. 4. Mean deliveries (n=6) of the drug combination (open bars) and 1% ethanol (filled bars) per 3-hr session as a function of fixed-ratio size. At each condition the two liquids were concurrently available under independent FR schedules of equal size. Note that the bars are stacked, not overlaid. Test conditions were conducted in the sequence depicted (left to right). For M-P1, to further confirm the results of the FR 16 retest condition, an additional FR size (FR 32) was tested.

TABLE 1

MEAN LIQUID DELIVERIES AT EACH FR SIZE AS A PERCENTAGE OF BASELINE (FR 1) VALUES*

	M-C		M-A		M-CR		M-P1	
	C	P	C	P	C	P	C	P
FR 16			60%	2%			134%	63%
FR 8	96%	6%	82%	1%	81%	132%	156%	47%
FR 4	109%	33%	90%	76%	77%	116%	157%	109%
FR 2	103%	56%	105%	83%	95%	140%	93%	139%
FR 1	100%	100%	100%	100%	100%	100%	100%	100%
FR 2	112%	45%	89%	115%	95%	68%	92%	47%
FR 4	101%	38%	91%	68%	93%	64%	150%	22%
FR 8	104%	5%	95%	5%	88%	44%	144%	24%
FR 16			58%	5%			126%	29%
	C	E	C	E	C	E	C	E
FR 16			44%	4%			2926%	3%
FR 8	81%	10%	75%	6%	135%	1%	2203%	67%
FR 4	90%	29%	87%	28%	147%	7%	298%	114%
FR 2	98%	110%	94%	73%	104%	62%	70%	109%
FR 1	100%	100%	100%	100%	100%	100%	100%	100%
FR 2	103%	37%	94%	41%	118%	98%	146%	93%
FR 4	94%	6%	84%	50%	65%	75%	154%	148%
FR 8	76%	6%	67%	37%	139%	3%	128%	144%
FR 16			46%	13%			2207%	11%
FR 32							2318%	5%

*C = combination, P = pentobarbital, E = ethanol.

the amount of behavior maintained by the two liquids generally increased with increases in FR size.

Table 1 presents another way of analyzing these data. Numbers of deliveries of each liquid at FR 1 were defined as 100% values. The numbers of deliveries of each liquid at each FR size were then related to the number at FR 1, by expressing them as percentages of FR 1 values. With increases in FR size, the drop in this percent measure was generally much greater for the single-drug liquids than for the drug combination. This effect was generally independent of whether FR sizes were tested in decreasing or increasing order. (The extra final test condition at FR 32 for Monkey M-P1 when ethanol was the single-drug liquid was conducted because of the sudden shift in relative maintenance of behavior by ethanol and by the drug combination that accompanied the shift in FR size from FR 8 to FR 16; the test at FR 32 was performed to confirm the results obtained at FR 16.)

DISCUSSION

The reinforcing effects of a combination of pentobarbital and ethanol were greater than the reinforcing effects of either drug alone. This conclusion is based on the relative rates of self-administration behavior maintained by the different drug solutions when they were concurrently available under identical fixed-ratio schedules during the first phase, and on the relative persistence of behavior maintained by the different solutions with increases in FR size in the third phase. A number of alternative interpretations of the findings can be ruled out. First, the results are not an artifact of sequence effects, since the order of presentation of liquids was counterbalanced. Nor are the results due to side preferences, since the sides on which the solutions were available were alternated. Finally, the results are not due to differences in exteroceptive stimuli, since discriminative stimuli (blinking lights) were the same for both sides.

A goal for future experiments is to analyze the interaction between the reinforcing effects of 1% ethanol and 1 mg/ml pentobarbital (the nature of the interaction may be different at other ethanol and pentobarbital concentrations). This interaction could be infra-additive (e.g., $1+1=1.5$), linearly additive (e.g., $1+1=2$), or supra-additive (e.g., $1+1=3$) [see (22)]. This analysis is constrained by limitations in measuring reinforcing effects: Statements can be made regarding ordinal rankings of reinforcing effects, but rankings based on interval or ratio measurement units are not possible. Thus, comparisons of reinforcing effects are limited to statements that one specific quantity of a reinforcer produces effects equal to, greater than, or less than those of a particular quantity of a second reinforcer. To analyze an interaction between 1% ethanol and 1 mg/ml pentobarbital, their reinforcing effects relative to one another must be determined. This could be accomplished by scheduling the two liquids concurrently, thereby identifying the one that maintains higher response rates (14,15). For purposes of explication, assume that in such a hypothetical test the relative reinforcing effects of 1 mg/ml pentobarbital are greater than those of 1% ethanol (i.e., when concurrently available, the pentobarbital solution maintains considerably higher response rates than the ethanol solution). This hypothetical outcome is shown in Expression A:

A. 1 mg/ml pentobarbital > 1% ethanol

One could then test for violations of predictions based on linearly additive effects. The assumption of linearly additive effects means that the addition of an equal value to both sides of the expression will not affect the inequality relationship. If 1% ethanol is added to each component, Expression B is obtained:

B. 1 mg/ml pentobarbital + 1% ethanol > 2% ethanol

If an empirical test of the relation in Expression B revealed the relative reinforcing effects of the 2% ethanol solution to be equal to, or greater than, those of the drug combination, then the effects of adding 1% ethanol to 1 mg/ml pentobarbital would be known to be infra-additive. (The results of the first phase of the present study demonstrated that the relative reinforcing effects of the combination are greater than those of either drug alone; these findings rule out the possibility that a preference for 2% ethanol could be due to the reinforcing effects of the combination being either equal to or less than those of 1% ethanol.)

Given the assumption of linear additivity of reinforcing effects, a similar inequality must be true if 1 mg/ml pentobarbital is added to each side of Expression A. This is represented in Expression C:

C. 2 mg/ml pentobarbital > 1% ethanol + 1 mg/ml pentobarbital

If the results of an empirical test showed that the relative reinforcing effects of 2 mg/ml pentobarbital were equal to or less than those of the drug combination, then the addition of 1 mg/ml pentobarbital to 1% ethanol would be known to be supra-additive. (This follows from the results obtained in the first phase of the present study, which demonstrated that the reinforcing effects of the drug combination are greater than those of 1 mg/ml pentobarbital.) As illustrated in Expressions B and C, it is possible that the reinforcing effects of the combination may be asymmetric with respect to the reinforcing effects of the individual drugs (i.e., adding 1% ethanol might yield linearly additive effects whereas adding 1 mg/ml pentobarbital may give supra-additive effects). The hypothetical relations just described illustrate how an analysis of the relative reinforcing effects of drug combinations can proceed.

Increased behavioral effects due to combinations of ethanol and barbiturates have been noted in several studies. In one study, increased reinforcing effects were seen when rats intravenously self-administered combinations of pentobarbital and ethanol (3); low doses of each drug, which did not maintain responding by themselves, did maintain responding when combined. In the DeNoble *et al.* study (3), unlike the present study, different drugs, including drug combinations, were available only sequentially, not concurrently. In another study the discriminative stimulus effects of ethanol-barbiturate combinations were examined: A combination of low doses of each of the two drugs produced discriminative stimulus effects even though the low dose of each drug alone was not discriminable from saline (1). Results of these studies, which did not use the oral route, aid in excluding the possibility that the findings of the present study were due solely to a change in the palatability of the pentobarbital solution which might have been produced by the addition of 1% ethanol.

Pharmacokinetic and pharmacodynamic interactions between ethanol and barbiturates have been reported, and there are a number of ways that such interactions could lead to increased reinforcing effects. For example, ethanol increases the rate of absorption of barbiturates (20). Thus, the greater reinforcing effects of the combination could be due to an increased rate of onset of CNS effects, that is, a shortened latency between drinking behavior and occurrence of these effects. A possible pharmacodynamic mechanism is the marked potentiation by ethanol of pentobarbital-stimulated $^{36}Cl^-$ uptake in isolated vesicles from the rat cerebral cortex (21). This effect occurred at ethanol concentrations below those which themselves directly stimulate $^{36}Cl^-$ uptake. Although we have not systematically investigated the matter, it is our impression based on visual observations that greater intoxication (i.e., greater degrees of ataxia and related motor behavior changes) is produced in our monkeys by a solution containing a combination of 1 mg/ml pentobarbital and 1% ethanol than by a solution containing only 1 mg/ml pentobarbital. A 1% ethanol solution never produces any observable intoxication in our monkeys.

In the third phase of the study, at higher FR sizes differences between reinforcers' effects on behavior emerged that were not evident, or were less evident, at lower FR sizes. These findings support the notion that differences in the relative reinforcing effects of concurrently available reinforcers may be more evident at higher than lower FR sizes (14). At low FR values, where both concurrently available drug solutions maintained behavior, the effects on behavior of other variables such as side preferences may be more evident (15). There are multiple examples of differences in relative reinforcing effects emerging only at higher ratios. For instance, in a previous study (11), differences between intermediate and higher pentobarbital concentrations in maintaining fixed-ratio responding appeared only at higher FR values. In another study, when a rhesus monkey was tested at FR 1, an 8% ethanol solution did not maintain higher response rates than water; however, when tested at FR 16, much higher rates were maintained by 8% ethanol than by water (5). Similarly, to obtain reliable differences between intravenously delivered cocaine and saline, it was necessary to increase the size of an FR schedule (8).

In summary, the reinforcing effects of pentobarbital solutions are increased by the addition of 1% ethanol. These findings have more general implications, in that a major determinant of polydrug abuse may be increased reinforcing effects produced by drug combinations. Such combinations may also be less expensive for the user than larger amounts of a particular drug, and/or may result in the emergence of novel characteristics. All of these factors may act to increase the frequency with which combinations of drugs are self-administered.

ACKNOWLEDGEMENTS

We thank Carl Brosman, Kelly Krattiger, Rachel Muir and Chimezie Ukaonu for their assistance in conducting the experiments, and an anonymous reviewer for comments on the manuscript.

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